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FORMULATION AND CHARACTERIZATION OF EXTENDED RELEASE MATRIX TABLETS OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

Venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants. Extended release tablets of venlafaxine to be taken once daily were formulated with venlafaxine hydrochloride equivalent to 75 mg of venlafaxine base. Matrix system based on swellable polymers was selected for extending the drug release. Different polymers and waxes viz. hydroxypropyl methylcellulose (HPMC), chitosan, Sodium alginate etc. were studied. Combinations of Chitosan with HPMC were also tried in order to get the desired extended release profile over a period of 24 h. FTIR studies revealed that there is no incompatibility between the drug and the selected polymers. The prepared tablets were evaluated for appearance, weight variation, thickness, hardness, friability, drug content and in vitro drug release at selected time intervals. The effect of drug to polymer ratio on *in-vitro* release was studied. Among all the formulations of venlafaxine, more extended release and desired drug release upto 24 hours was observed in the formulation (F8) containing sodium alginate and chitosan in 1:1 ratio ie., 97.76%, so it is considered as the best formulation in comparison to other formulations. The optimized formulation was subjected to stability studies at 40°C/70% RH and no significant changes were observed in the formulation.

Keywords: Venlafaxine, Swellable polymers, Chitosan, HPMC, Sodium alginate

INTRODUCTION:

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized"[1,2]. Appropriately designed extended-release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target tissue[3]. Matrix tablets are an interesting option when developing an oral controlled release formulation[4].

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The present study focuses on oral controlled-release dosage forms and types of various polymers are used to formulate matrix tablets. Venlafaxine Hcl is an effective and well tolerated antidepressant and is considered as first-line pharmacological treatment in patients with major depression. It is also used in the treatment of fibromyalgia. Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Plasma half-lives of venlafaxine and ODV are 5±2 hours and 11±2 hours, respectively. It has an oral bioavailability is 40% to 45%[5,6].

The present research work is aimed at improving bioavailability of the drug, reduce the dosing frequency and to improve patient compliance by formulating it as extended release tablets by using polymers such as chitosan, HPMC k 100 m and sodium alginate. As it has low half life it is a suitable candidate for extended release formulations[7].

MATERIALS AND METHODS:

Materials:

Venlafaxine Hcl was obtained as a gift sample from Alkem Pvt Ltd Mumbai. HPMC K100M and sodium alginate were purchased from Coloron Asia Pvt .Ltd. Chitosan, PVP K-30, Microcrystalline cellulose, Magnesium stearate and Talc were purchased from SD fine chem Pvt, Mumbai.

Methods:

Compatibility studies between drug and excipients:

The physical compatibility of Venlafaxine with various excipients was carried out with an aim to select suitable excipients for a stable and strong formulation. FTIR spectra of the drug and the drug with excipients were recorded in range of 4000-400 cm^{-1}. Compatibility studies were performed using FTIR spectrometer. The FTIR spectrum of the pure drug and physical mixture of the drug and excipients were studied.

Formulation development:

Drug and polymers were passed through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Binder (PVPK-30) was dissolved in isopropyl alcohol which is used as a granulating agent. Above drug-polymer blend is granulated by using binder solution. Other excipients as given in table-1 are added to the above mixture. Finally glidant (Magnesium Stearate) and lubricant (Talc) were added and mixed for 2min and compressed by using 8 mm round punches.

Pre-compression Parameters[8]:

1) Apparent Bulk Density:

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

2) Tapped Density:

Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (200). The tapped density was determined by the following formula.

Density = Mass/Tapped Volume

3) Percentage Compressibility (or) Carr's index (%):

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula and the nature of flowablity based on the compressibility values are given in the table-2.

$$\text{Carr's Index}(\%) = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped density}} \times 100$$

4) Hausner's Ratio:

It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density. The nature of flowablity based on hausner's ratio values are given in the table-3.

Hausner ratio = Tapped density/Bulk density

5) Angle of Repose:

The flow property was determined by measuring the Angle of Repose and the specifications for flow are given in table-4. 20gms of the sample was taken and was passed through the funnel slowly to form a heap. **T**he height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Angle of repose= $\tan^{-1}$ (h/r)

Where, h = height, r = radius

Evaluation of Tablets:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and *in vitro*-dissolution characters[9].

1. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

2. Hardness:

The resistance of tablet to chipping, abrasion or fracture under condition of storage, transportation and handling before usage depends upon its hardness. For each formulation, the hardness of 6 tablets was determined using the Schleuniger hardness tester. This tester operates in a horizontal position. An anvil driven by an electric motor presses the tablet at a constant load rate in contrast to a stationary anvil until the tablet breaks. A pointer moving along a scale indicator provides the breaking strength value/Hardness value.

3. Friability:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. The percentage friability was determined by the formula: % friability = $(W_1-W_2) / W_1 \times 100$

W_1 = Weight of tablets before test, W_2 = Weight of tablets after test

4. Weight variation test:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP as given in table-5. No tablet must differ by more than double the relevant percentage.

5. Content Uniformity:

The drug content of the matrix tablets was determined by standards and it meets the requirements if the amount of the active ingredient in each of 10 tested tablets lies within the range of 90% to 110% of the standard amount. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of venlafaxine HCl was transferred to 100ml volumetric flask containing 70ml of 6.8 pH phosphate buffer. It was

shaken by mechanical means for 1hr then it was filtered through Watsmann filter paper (no.1) and diluted to 100ml with 6.8 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 6.8 pH phosphate buffer and absorbance was measured against blank at 226 nm[10,11].

***In-vitro* drug release study:**

In-vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 12 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffers for further 10 h. 5ml of sample was withdrawn in different time intervels, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 226 nm, and cumulative percent drug release was calculated. The study was performed in triplicate[12].

Kinetic-models[13-15]:

In order to describe the drug release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: Zero order, first order, and Higuchi respectively.

$$Qt = Q0 + K0\ t \quad \text{..... (1)}$$

Where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1/2.303)\ t \quad \text{..... (2)}$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t\ ½ \quad \text{..... (3)}$$

Where, KH is the Higuchi rate constant.

Further, to better characterize the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas. $Q\ (t\text{-}l)\ /Q\alpha = KK\ (t\text{-}l)n$ ..... (4)

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where $Q\ (t\text{-}l)/Q\alpha > 0.6$, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if $0.5 < n < 1$, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ''best model'' was the one with the highest coefficient of determination (r^2).

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines. Following conditions were used for Stability Testing. 25°C/60% RH analyzed every month for period of three months. 30°C/75% RH analyzed every month for period of three months. 40°C/75% RH analyzed every month for period of three months.

RESULTS AND DISCUSSION:

Drug-Excipients Interaction Study:

From the FTIR spectrum as shown in figure 1 and 2, it was concluded that no significant shift in peak pattern in IR spectrum of drug and drug with polymer-excipient mixture which concludes that there is no incompatibility between drug and employed excipients and polymers.

Pre compression Studies:

The method employed for tabletting in this study was wet granulation for which the drug or the mixture of drug and polymer should possess good flow properties. Granules ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder blend, to achieve constant uniformity of tablet weight. From the results given in table-6 it was found that all the formulations possess good flow properties.

Post compression evaluation study:

The results obtained are represented in the table-7. Thickness of the formulation ranges from 2.01±0.02 to 2.06±0.04mm. Weight variation of all formulations showed satisfactory results. And it ranges from 349.4±0.4 to 350.7±0.1 mg, the percentage weight variation was within the pharmaceutical specifications. Hardness of all formulations was maintained in the range of 6-8 kg/cm^2. Friability of all formulations was less than 1% and it ranges from 0.11%±0.3 to 0.16%±0.23. Drug content of all formulations was in the range of 95.01% ± 0.2 to 99.88 %±0.2. All the results indicate that the prepared formulations comply with the inproecss specifications of tablets.

***In-vitro* drug release study:**

The results of *in-vitro* dissolution study are presented in the table-8. It was found that the formulations containing single polymers have shown the drug release upto 12 hours, and the polymers are used different combinations the release of the drug from the matrix tablets was slowed to a greater extant and the release continued upto 24hours. Of all the formulations containing polymers in different ratios, the formulation F8 containing sodium alginate and chitosan in 1:1 ratio have shown a slow and controlled drug release through the study, thus it is optimized.

Release kinetics:

The data obtained from the in-vitro dissolution studies of the optimized formulation F8 is fitted into various kinetic models to determine the mechanism of drug release, and it was found that the drug release from the matrix is by first order kinetics and as the slope value from the Korsmeyer peppas model is less than 5, it indicates that drug release is by fickian diffusion mechanism. The regression co-efficient and slope values are given in the table-9.

Stability study:

From the above stability results data given in the table-10, we conclude that optimized formulation was stable upto 120 days (i.e. 3 months) and it doesn't show any physicochemical changes.

Table.1: Composition of Venlafaxine HCl Extended release matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Venlafaxine HCL	75	75	75	75	75	75	75	75	75	75
Chitosan	50	100	---	---	---	---	50	50	---	25
HPMC K 100 M	---	---	50	100	---	---	50	---	50	25
Sodium alginate	---	---	---	---	50	100	---	50	50	100
Microcrystalline cellulose	140	90	140	90	140	90	90	90	90	90
PVP K-30	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2
Iso propyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total wt (mg)	225	225	225	225	225	225	225	225	225	225

Table.2: Percent Compressibility limits with respect to flow ability

%Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair
23-25	Poor
33-38	Very poor
More than	Very very poor

Table.3: Hausner's ratio limits

Hausner's ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

Table.4: Angle of Repose limit

Flow properties	Angle of repose (θ)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	> 66

Table.5: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

Table.6: Precompression parameters for the prepared granules

Parameter	Angle of repose	Bulk density (gm/cc)	Tapped density (gm/cc)	% compressibility	Hausner's ratio
F1	25°43'±0.1	1.041±0.3	1.16±0.1	11.4	1.114
F2	26°46'±0.2	1.02±0.4	1.12±0.2	9	1.09
F3	23°31'±0.1	1.01±0.2	1.11±0.1	9	1.09
F4	26°89'±0.17	1.02±0.28	1.11±0.21	8	1.08
F5	29°14'±0.1	0.96±0.24	1.03±0.27	7	1.07
F6	28°14'±0.2	0.95±0.24	1.03±0.27	9.5	1.095
F7	29°12'±0.1	0.94±0.2	1.03±0.2	9	1.095
F8	24°21'±0.1	0.96±0.2	1.04±0.2	8	1.08
F9	27°14'±0.4	1.041±0.3	1.16±0.1	11.1	1.114
F10	25°13'±0.4	1.02±0.4	1.12±0.2	9	1.09

Table.7: Post compression parameters for the prepared tablets

Formulation code	Thickness (mm)	Hardness Kg/cm^2	Weight variation (mg)	Friability (%)	Drug content (%)
F1	2.01±0.06	8.9±1.4	350.6±0.4	0.12%±0.2	95.01%±0.2
F2	2.04±0.01	7.4±1.2	349.4±0.4	0.16%±0.23	96.4%±0.4
F3	2.06±0.04	8.2±1.2	349.9±0.7	0.15%±0.19	98.7%±0.3
F4	2.03±0.01	6.9±0.9	350.7±0.1	0.15%±0.26	98.8%±0.2
F5	2.01±0.02	8.4±1.9	349.6±0.3	0.15%±0.22	99.8%±0.3
F6	2.05±0.03	8.1±1.7	350.1±0.2	0.12%±0.1	99.19%±0.2
F7	2.01±0.02	8.2±1.5	349.8±0.9	0.11%±0.4	99.18%±0.2
F8	2.05±0.05	7.3±1.6	350.5±0.8	0.11%±0.5	99.88%±0.2
F9	2.05±0.02	8.2±1.4	350.6±0.1	0.11%±0.3	99.18%±0.2
F10	2.05±0.02	8.2±1.5	350.2±0.1	0.11%±0.8	99.58%±0.2

Table.8: *In-Vitro* Dissolution Studies of Extended release Tablets of Venlafaxine

Time(hrs)	F1	F2	F3	F4	F5	F-6	F-7	F-8	F-9	F-10
0	0	0	0	0	0	0	0	0	0	0
1	32.91	34.92	58.91	55.83	58.44	56.29	32.37	28.35	53.83	47.92
2	56.24	48.92	67.24	64.26	66.83	63.21	42.47	39.81	61.26	58.92
4	62.84	59.21	78.84	73.87	76.47	75.38	59.28	50.47	70.87	68.21
6	80.78	74.93	89.78	86.38	88.74	87.78	74.41	64.87	84.38	79.92
10	92.72	89.72	97.72	93.71	96.82	95.36	88.26	79.38	92.71	86.72
12	96.38	98.92	99.51	98.27	99.64	99.90	92.49	88.61	95.42	90.92
24	-	-	-	-	-	-	95.85	98.76	97.29	94.17

Table.9: Release kinetics for F8 formulation for extended release tablets

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	3.634	-0.0206	19.0311	0.4125
Intercept	29.479	2.6603	14.3465	1.4698
Correlation	0.8700	-0.9960	0.9731	0.9907
R^2	0.7569	0.9920	0.9469	0.9814

Table.10: Stability Studies of Optimized Formulation

Time in days	Physical changes	Mean % drug content ± SD	
		25°c	30°c
01	No Change	98.76±0.49	98.74±0.49
15	No Change	98.75 ± 0.45	98.72 ± 0.42
30	No Change	98.75± 0.39	98.72 ± 0.37
45	No Change	98.75 ± 0.76	98.71 ± 0.41
60	No Change	98.71 ± 0.81	98.70 ± 0.37
75	No Change	98.69 ± 0.31	98.68 ± 0.81
90	No Change	98.67 ± 0.43	98.69 ± 0.91
105	No Change	98.67± 0.51	98.69 ± 0.15
120	No Change	98.67 ± 0.48	98.69± 0.27

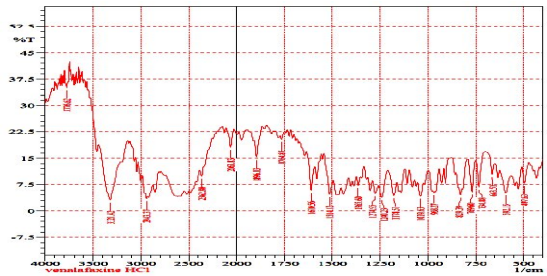

Figure.1: IR spectrum of Venlafaxine

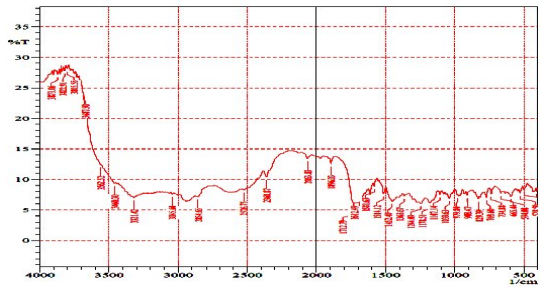

Figure.2: IR spectrum of Drug with polymer-excipient mixture

CONCLUSION:

The venlafaxine extended release tablets were successfully prepared by wet granulation method by employing polymers such as HPMC K 100, Sodium Alginate and Chitosan. The prepared granules exhibited good flow property and the tablets prepared by using granules produced tablets with the required specifications with fewer variations. The prepared tablets complied with in-process quality control tests. Based on the *in-vitro* dissolution studies, and their *in-vitro* behavior formulation F8 containing chitosan and sodium alginate were found to be the best one with desired drug release throughout the test period. Various kinetics models have being used to determine the drug release and it has shown that drug release is by First order kinetics and mechanism of drug release is by fickian diffusion. Based on the stability data it was found that there was no significant change in the prepared tablets during the test period of 120 days. Thus finally concluded that formulation F8 fulfills the objective of the study ie., increases the bioavailability, decreases dosing frequency and increases patient compliance.

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